Government Regulations and the Use of Drugs

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■ *I have tried to trace the new drug development pattern from 1766, when Withering obtained his medical degree, to the present.*

The role of governmental authority as defined by the 1962 Kefauver-Harris amendments to the 1906 law and the subsequently issued regulations has been summarized. Four phases of testing in man have been detailed.

Something of the scientific or research capability of the pharmaceutical industry has been presented.

It is concluded that in the period of over two hundred years of medical education in the United States, the university hospital has become more and more the focus of medical research, teaching and practice in the community. The safety and effectiveness in the use of drugs in the future will depend upon the liaison and rapport of the industry physicians, government officials and the university hospital teacher-clinical investigators (phase 1 and 2) in designing the most critical studies of the safety and effectiveness of new drugs.

Whether the medical profession as we know it will participate more in the future than has been possible since 1962 in mass clinical trial (phase 3) before new drug approval by governmental authority remains to be seen.

The final approbation or disapproval of a drug after NDA approval (phase 4) will continue to be in the hands of the participating physician as long as he can establish scientifically that the drug is the best possible agent for him to use in healing the sick and comforting the dying.

THE PURPOSE of this presentation is to crystallize the most cogent facts and mention certain of the opinions that have been expressed* with regard to government regulations and the use of drugs.

Specifically, I want: (a) to clarify the current regulations regarding clinical investigation of a nonintroduced (new) drug; (b) to define more precisely not only the dependence of industry on the scientific community, and particularly the physicans in academic medicine who are qualified to test new drugs in man, but also the obligation of those clinical investigators as well as all physicians in clinical medicine to report all pertinent informa-

*Reference Nos. 3, 4, 6, 7, 12, 16, 20, 25.

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tion on new drugs to the governmental officials in the Food and Drug Administration (FDA) of the United States Department of Health, Education and Welfare; and (c) to mention the need for clarification of the role of the qualified physician in clinical medicine in the approbation or disapproval of a new drug before the FDA has sanctioned the chemical compound for marketing.

Government laws effective 1 February 1966, regulating the addictive aspects of drugs (drug abuse control) are not a concern of this synopsis; the emphasis here relates to the changes facing physicians in order to better evaluate new drugs and speed the flow of needed therapeutic tools to their patients.

The 1962 amendments (Public Law 87-781)[23] *do not represent an entire revision of the Federal Food, Drug and Cosmetic Act.*

Since the passage of the 1938 law, the introduction of a new drug into the United States market has required the approval of the FDA through a new drug application (NDA) approval. Up until 1962, if the FDA did not take action within six months after the application was filed, the manufacturer automatically was allowed to market the drug. Now there is no longer any automatic clearance of new drugs for the market by lapse of time without FDA action, as under the previous law. A new drug cannot be marketed until the FDA approves it as meeting the requirements for safety and effectiveness.

The law recognizes that medical research must go on. Under the 1962 amendments, experimental drugs are exempted from the safety clearance requirements of the law when shipped to qualified investigators for research purposes. However, the testing of new drugs and antibiotics on humans can be prevented under the law unless specified safety conditions are met. In order to meet these safety conditions, the manufacturer must report to the FDA by means of a "Notice of Claimed Investigational Exemption for a New Drug" (IND). This is a form which the regulations have precisely defined (FD1571) in order that all the pertinent facts about the new compound be submitted under ten specific headings. As soon as this is filed, the sponsor or manufacturer can begin research on the drug in man, all research in the United States up to this point having been preclinical and chiefly toxicological to document the safety aspects.

The amendments spell out the direction the planned investigation must follow. Phase 1 starts when the new drug is first introduced into man, and this is denoted as human pharmacology. Phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes (selected therapeutic trial). Phase 3 is the stage of inquiry bearing on the assessment of the drug's safety and effectiveness. Specifically, the sponsor must establish the range of optimum dosage schedules in the diagnosis, treatment or prophylaxis of *groups* of subjects involving a given disease or condition (mass therapeutic trial). The amendments require that the sponsor report the progress of the investigators to the FDA once yearly. They also stipulate immediate documentation of any serious or life-threatening adverse reactions. At this point, as the pattern of the results of clinical studies takes form, the sponsor assembles the data and presents them to the FDA for NDA. If approved, the compound is marketed.

The amendments require the sponsor or manufacturer to report to the FDA any information on adverse effects or other new clinical experience with new drugs and antibiotics after they are marketed (phase 4). In practice, physicians contact the manufacturer for information. The Medical Department physicians then attempt to develop a complete Drug Reaction Report form with the attending physician's assistance. This form is then transmitted by the manufacturer to the FDA.

Signed agreements from investigators—FD1572 for phase 1 and 2, FD1573 for phase 3—must be obtained by the sponsor and submitted to the FDA, stipulating that the proposed investigations will be under the personal supervision of the investigator signing the form, that the experimental drugs will not be supplied to others and that experimental use on humans is permitted only if the clinical investigator agrees to tell his patients about the experimental status of the drug. Commissioner James L. Goddard recently has spelled out the exceptions to these requirements.[9]

The use of drugs in man is like a tool or an instrument of the physician for the treatment of the sick and protection of the healthy.

The medical doctor participates at every stage in the creation, development, evaluation and use of a drug.[5] The omnipresence of governmental authority's interest together with that of the university medical school in all aspects of therapeutics is borne out by the history of medical education and medical practice in the United States from colonial times to the present.[8,22] The first concern shown by governmental authority, about a "receipt [re-

cipe] of curing cancer," was recorded in the 1748 proceedings of the House of Burgesses of the General Assembly of Virginia.[11]

Four periods might be mentioned, based on the role governmental authority has played in relation to control of the physician's therapeutic tools: 1748-1906, 1906-1938, 1938-1962, 1962-1966. For each period, certain questions can be raised as to what was done and what was left undone at that time.

1748-1906 William Withering was born in 1741 and graduated in Medicine at Edinburgh in 1766. Up until 1906 when the chemist Wiley was the main force behind Congress passing the first food and drug control law, Withering might be considered to be a representative, in an extraordinary manner, of the developer of a new drug of that time. In his experience he embodied an understanding of a clinical need and of the folklore of his community—a "family receipt" [recipe] for cure of dropsy, kept a secret by an old woman in Shropshire. He was an unusual student of botany, having published a treatise on plants in his region of England in 1776, and suspected the active ingredient of the dropsy cure to be foxglove *(Digitalis purpurea)*. Finally, he used the approach of the modern clinical investigator as revealed by his monograph,[26] with its case histories of *each* patient to whom the drug was given.

In the United States a physician was instrumental in starting the *Pharmacopoeia of the United States* in 1820, the American Medical Association was founded in 1847, and in 1875 the first university hospital (Hospital of the University of Pennsylvania) was established—all key events breaking up the long period of growth in this country of medical education and medical practice. A nihilistic approach to drug usage in the 19th century was described by Osler, one of America's great medical teachers and thinkers.[19] Already in Withering's time apothecaries were on the scene, and they played an unusually prominent role in the use of drugs from colonial times on, into the 20th century.[22]

1906-1938 The influence of pharmacists persisted almost up to 1938, when the first food and drug law was completely rewritten in the attempt to provide a more realistic basis of regulation by governmental authority. In this period the relationship between the all-encompassing physician, as Withering was, and the sick person was giving way to the relationship of the patient, physician and the drug manufacturer who supplied the substance to be compounded by the pharmacist. Between 1905 and 1935 basic new drugs were added to the *U.S. Pharmacopoeia* at an average rate of six per year.[18] From 1905 to 1956, the American Medical Association's Council on Pharmacy and Chemistry, later the Council on Drugs, also passed on drugs before they could be advertised in the Association's publications and listed in its books.[4]

The Federal Pure Food and Drug Act passed in 1906 was basically unchanged until 1938. It prohibited sale in interstate commerce of adulterated or misbranded products. This law was significantly strengthened in 1938 after the tragedy of the distribution, without animal testing, of a sulfa drug elixir in the southeastern United States in 1937. The vehicle, diethylene glycol, proved to be poisonous and was causally related to the death of about one hundred patients before the compound could be removed from the market.

1938-1962 The introduction of sulfa drugs into medical practice in the United States by Perrin Long and Eleanor Bliss at Johns Hopkins Hospital in 1936 might be considered to be the true beginning of the 1938-1962 period. The 1937 tragedy brought government more into control of drugs as far as safety was concerned.

1962-1966 There is still the basic relationship of physician, patient, pharmacist and drug in concert with governmental authority. In the period from 1945 to the present, we have seen an upsurge in "public interest," together with greater dissemination of "product information" to the physician by the profit-motivated pharmaceutical industry.

The most outstanding feature undoubtedly is the amount of sales dollars put into the research and development efforts of the United States drug industry. In 1950, 39 million dollars was spent and the preliminary estimate for 1966 was 355 million. In this period, company financed research and development rose from 4 per cent to nearly 10 per cent of sales.*

Research capabilities of the pharmaceutical industry are divided into three major categories: (a) preclinical, before IND filed, (b) after IND filed, clinical or human pharmacology and selected therapeutic trial, (c) mass clinical trial for NDA and post-NDA marketing surveillance.

*From Chart V, *Key Facts on the U. S. Prescription Drug Industry*, January 1966, distributed by Pharmaceutical Manufacturers Association, Washington, D.C. 20005.

In 1966 the problem of judging whether a new drug application (NDA) is to be approved is more complex than ever before.

In a statement presented by George P. Larrick[17] on 24 March 1964, the then FDA Commissioner explained "How the Food and Drug Administration Evaluates New Drug Applications." Larrick pointed out that, "The average practicing physician, skilled as he may be in making daily decisions with regard to individual drugs to be administered to individual patients, is not necessarily qualified to make the broader decisions about permitting nationwide marketing of a drug."

The FDA must decide now whether the compound is *effective* for the indication as well as safe. Effectiveness is relatively simple to measure in testing an antihypertensive agent in patients. But what about the problem of evaluating quantitatively the effectiveness of a compound proposed to allay the symptoms of the anxious patient—for example, meprobamate? This is controversial.*

Or stated in another way, how probable in the years ahead is the participation of more clinicians in the phase 3 testing of new drugs? That a change from the period of 1962-1966 is needed seems clear. Both James Appel[1] and James Goddard[9] have stressed the desirability of more qualified physicians taking part in the assessment of new drugs in the gap between pharmacology and therapeutics.[12] The degree of dissatisfaction of clinicians with the complexity of the paper work associated with drug investigation and the precise hindrances needs to be documented now.[13] The survey published by William Kirby in 1964 was a limited sampling of the reaction of certain physicians in academic medicine and reflected the early 1963 apprehension.[15] Appel's suggestion that the council of the specialty society is the logical arena in which physicians might work toward a change seems realistic.[1]

Wolferth set forth his ideas about the possible contribution of clinicians in medical research in 1959.[27] At the risk of diminishing the importance of the entire essay, one paragraph out of context is quoted:

"Clinicians occupy a strategic position sometimes overlooked by those who write about how medical research should be done and who should do it. Clinicians are close to the raw material of clinical science. They sit by the bed side, agonize over the patients who look to them for help, and ask themselves questions that might not occur to the most analytical career investigators. In the past, such questions have constituted an important source of stimulation to clinical science as well as technologic research. One wonders whether Addison and Mackenzie would have done as well as full-time career investigators."

It would seem a tragic loss to American medicine if the 1962 regulations impede or prevent the contributions of future clinical scientists of the Wolferth mold to the clinical assessment of new drugs.

Krantz[16] has expressed the opinion that the part of the 1962 law regarding the establishing of efficacy should be changed. Another opinion is that expressed by the former Medical Director of the FDA, Joseph F. Sadusk, Jr.[21] He urged that present drug legislation be thoroughly enforced before any new measures are adopted.

"The basic Food, Drug and Cosmetic Act of 1938," Dr. Sadusk said, "together with its several Amendments up to and through 1965, now give the Food and Drug Administration sweeping authority to monitor and control the development, production and use of drugs. It assures us that these drugs will be of high quality and that they will be effective. It provides for the continuing surveillance of drugs so that if there is a significant change in the status of any drug the physician can be informed promptly. But in carrying out the intent of the law there are a number of problems, chief among which is the careful planning and effort which must go into the implementation of that law. Here, the scientific community, the pharmaceutical industry and the Food and Drug Administration itself must develop a degree of expertise which was not dreamed of a decade ago. Organizational structures for such scientific and regulatory purposes are not accomplished in a year or two—the matter is so complex and properly qualified manpower is in such short supply that a half decade or more will be needed to fully implement the law. It would be a mistake to believe that this can be done in less time. Furthermore, the mission cannot be achieved successfully by any one of the group alone. The goal will be reached only as a joint and coordinated effort of the medical community, the industry, and the government. Fortunately, the Congress has amply supported this effort by substantial appropriations of funds but the real bottleneck remains that of manpower."

What, then, in the years ahead, is the prospect for more practicing physicians assisting in the de-

*Reference Nos. 2, 10, 14, 24.

velopment of new drugs in phase 3 before they are approved for marketing by the FDA? From what has been presented, there seems to be an increasing awareness of the potential contribution by the clinician. However, the 1962 law states that clinical investigations should be carried out by "experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved." Change to the extent that more expert clinicians are involved in evaluating new drugs seems obvious. What is also clear is that the final approbation or disapproval of a drug after NDA approval (phase 4) will continue to be in the hands of the practicing physician as long as he can establish scientifically that the drug is the best possible agent for him to use in healing the sick and comforting the dying.

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